infection whit gB1+gB3 and gB2 + gB3. HCMV disease developed in 2 patients, characterized for gastrointestinal disease and these two patients had infection with a mixture of HCMV gB genotypes.
Conclusions: in this study the most prevalent genotype in patients with HCMV active infection was gB genotype 1 and moreover, the mixture of HCMV gB genotypes was associate with gastrointestinal disease. However, this study is limited due to the small number of patients, thus making it difficult to draw a firm conclusion regarding the distribution of HCMV genotypes and their possible association with outcome. Nevertheless, these results may be taken as a preliminary report on the prevalence of different HCMV gB genotypes in a Brazilian allogeneic HSCT population with active HCMV infection.

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A PHASE I STUDY OF CLOFARABINE PLUS HIGH DOSE MELPHALAN AS A CONDITIONING REGIMEN FOR ALLOGENEIC TRANSPLANTATION

Kirschbaum, M.H., Stein, A.S., Nakamura, R., Auayporn, N., Popplewell, L., Delioukina, M., Chen, R., Snyder, D., Conrad, J., Frankel, P., Forman, S.J. City of Hope National Cancer Center, Duarte, CA

Background: Reduced intensity regimens for allo transplant successfully replaced the alkylating agent cyclophosphamide with the purine nucleoside antimetabolite, fludarabine, an immunosuppressive with a milder toxicity profile. Clofarabine is a purine nucleoside analogue designed to exploit a double halogen strategy which confers resistance to adenosine deaminase and makes the drug more efficient than fludarabine at inhibiting ribonucleotide reductase and disrupting mitochondrial function, leading to apoptosis.
Aims: To evaluate a clofarabine containing regimen as conditioning for allogeneic stem cell transplant.
Methods: phase I dose escalation: clofarabine (dose level one = 30 mg/m^2, dose level two and three = 40 mg/m2) IV daily days –7 to day –3 infused over 30 minutes IV, plus Melphalan (dose level one and two, 100 mg/m^2, dose level three, 140 mg/m2) administered over 30 minutes IV on day –2. Related or unrelated allogeneic stem cells were infused on day 0. GVHD prophylaxis: initially CSP plus mycophenelate, then tacrolimus plus sirolimus was adopted as per COH standard of care. Patients age ≥ 18 years with AML, ALL, MDS in CR1, CR2 or in relapse (up to 50% marrow blasts), not deemed eligible for standard transplant regimens, or at high risk for relapse, are eligible.
Results: We report on the first 2 dose levels. 10 eligible patients, all with AML, have been treated thus far, 4 Males, 6 Females, with a median age of 62 years (39 – 65). 5 patients were in CR1, 2 patients were in CR2, and 3 patients were transplanted in relapse. Grade 3 non-hematologic toxicities included fatigue, elevation of AST and LFT, diarrhea, and hyponatremia and mucositis (in one patient). No dose limiting toxicities (DLT) were seen in level one. One patient in dose level 2 died prior to engraftment due to hepatic, renal, and infectious toxicities; that dose level has been expanded thus far to seven patients and no further DLT have been seen (one accrued patient was ineligible due to mismatch). Three patients in relapse received an unrelated donor graft, had complete engraftment and achieved remission. Engraftment data is presented in the table below. Mild acute skin graft versus host disease (GvHD) was seen in two patients, with mild gut GvHD responsive to steroids seen in one patient, and mild chronic GvHD in one patient.
Conclusion: The combination of clofarabine and melphalan is an adequate conditioning regimen leading to complete engraftment of allogeneic stem cells.

Dose Level	Patient	Days* to ANC ≥ 0.5x109/L	Days* to PLT ≥ 100	Months Follow-up**	Status
1	1	14	15	20	Remission
1	2	14	13	20	Remission
1	3	24	23	18	Remission
2	4***			1	Expired
2	5	13	13	16	Remission
2	6	17	13	10	Remission
2	7	12	14	8	Remission
2	8	16	14	6	Remission
2	10	12	13	1	Remission
2	11	16	15	1	Remission
	median	14	14	9	

* - From Transplant ** - Days from transplant to relapse/death or last contact *** - Patient expired prior to engraftment.

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DYSGLYCEMIA FOLLOWING GLUCOCORTICOID THERAPY FOR ACUTE GRAFT VS. HOST DISEASE ADVERSELY AFFECTS TRANSPLANTATION OUTCOMES

Pidala, J.[1], Kim, J.[2], Alsina, M.[1], Ayala, E.[1], Field, T.[1], Fernandez, H.[1], Kharfan-Dabaja, M.[1], Ochoa, L.[1], Perez, L.[1], Perkins, J.[1], Tomblyn, M.[1], Anasetti, C.[1] [1]Moffitt Cancer Center, Tampa, FL; [2]Moffitt Cancer Center, Tampa, FL

Disordered glucose metabolism is a common complication of glucocorticoid therapy for acute graft vs. host disease (aGVHD) after allogeneic hematopoietic cell transplantation (HCT). We aimed to examine the independent impact of serum glucose parameters (maximum, minimum, mean, and standard deviation) on outcomes in a series of 173 recipients of HCT who were treated with glucocorticoids for aGVHD. Median onset of aGVHD was 23 days (range 5 – 1112). Patients were treated with primarily 1 mg/kg of glucocorticoids for biopsy-confirmed aGVHD. The median duration of glucocorticoid therapy was 271 days (range 15 – 1632). Glucose values were obtained from glucocorticoid initiation date to death or last follow up, resulting in a total of 13,170 values. The median (range) values for each parameter were: maximum 292 mg/dL (128 – 694), minimum 75 mg/dL (34 – 142), mean 146 mg/dL (86 – 327), and standard deviation 47 mg/dL (12 – 108). Baseline diabetes mellitus predicted significantly greater maximum, mean, and standard deviation. With a median follow up of 18 months, median overall survival (OS) was 16 months (95% CI 11 – 34). On multivariable analysis, maximum glucose significantly predicted OS and non-relapse mortality (NRM). Increased variability also predicted OS and NRM. Those with minimum glucose values of (0 – 60 mg/dL) had increased NRM. Values for minimum glucose demonstrated a non-linear relationship with OS: those with minimum glucose of (0 – 60 mg/dL) as well as those (81 – 150 mg/dL) had significantly worsened OS compared to (61 – 80 mg/dL). Minimum glucose of (81 – 150 mg/dL) was associated with significantly increased risk for relapse. These data demonstrate the adverse effect of dysglycemia in patients treated with glucocorticoids for aGVHD, and argue for stringent glycemic control in this setting. Further efforts to reduce the burden of aGVHD, and its associated treatment with glucocorticoids are paramount.

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ALLOGENEIC HEMATOPOIETIC STEM TRANSPLANTATION DOES NOT ERASE THE IMPACT OF THE NEW PROGNOSIS CLASSIFICATION IN AML AND THE NEGATIVE INFLUENCE OF EVI1 AND FLT3 ITD MUTATIONS

Michallet, M., Sobh, M., Hayette, S., Charlot, C., El Hamri, M., Tedone, N., Nicolini, F.E., Ducastelle, S., Baracco, F., Tigaud, I., Thomas, X. Edouard Herriot Hospital, Lyon, France

We studied 78 patients who underwent an allogeneic HSCT for AML and for whom we had cytogenetics and molecular markers.

There were 73 de novo and 5 secondary AML. Regarding cytogenetics and molecular markers: 6 were in favourable, 29 in intermediate and 38 in unfavourable group and we found 5 Flt3 mutated, 22 Flt3 ITD+, 4 MLL mutated, 13 Hoxa9 mutated, 10 Evi1 mutated, 34 Wt1 mutated and 17 NMP mutated, 11 patients were in the good prognosis group and 61 in the poor prognosis group. At transplant, 42 patients were in CR1, 22 in > CR1 and 14 in progressive disease, 49 received a myelo-ablative and 29 a non myelo-ablative conditioning. As HSC source, 27 received PBSC, 46 bone marrow and 5 cord blood cells. With a median follow-up of 32 months, the 3-years overall survival was 45% ±12 with no significant impact of age, FAB classification, kind of AML (de novo vs secondary), HSC source (PBSC vs BM), Flt3, MLL, HoxA9, NMP and WT1 mutations. We found a difference of survival but not reaching the significance for Flt3 ITD [27.5% ±20 (mutated)vs 52% ±12 (non mutated), p = 0.09] and a significant difference of survival for Evi1 [48.5% ±14 (non mutated) vs 22.5% ±26 (mutated), p = 0.04]. We also showed a difference of survival not reaching the significance according to cytogenetics with 83% ±30 for favourable, 53% ±20 for intermesiate and 28% ±16 for unfavourable although we observed a very significant difference of OS according to the new prognosis classification between the good prognosis group with 81% ±24 and the poor prognosis group with 38% ±14 (p = 0.04). In addition, we found a significant better survival for patients in 1st CR (60% ±16) vs > CR1 (31% ±22) or in progressive disease (24% ±22)(p = 0.009) and a significant difference of survival according to conditioning with 54% ±16 for myelo-abative vs 11% ±18 for RIC (p < 0.0001).The multivariate analysis showed a significant impact on OS of the new prognosis classification [HR = 3.62 [95%CI 2.89-4.35] (p = 0.03)], disease status at transplant [HR = 151 [95%CI 1.28-1.74] (p = 0.07)], kind of conditioning [HR = 0.32 [95%CI 0-0.7] (p = 0.003)], Evi1 [HR = 0.33[95%CI 0-0.8] (p = 0.02)] and Flt3 ITD [HR = 0.43 [95%CI 0.07-0.78] (p = 0.02)].

The OS after allogeneic HSCT remains very poor for patients having Evi1 mutation and Flt3ITD for whom it is fundamental to propose new strategy of allogeneic HSCT in 1st CR as for example allotransplant after FLAMSA regimen or haplo-identical allogeneic HSCT.

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CD3 CELL DOSE AND OUTCOME AFTER ALLOGENEIC STEM CELL TRANSPLANTATION

Farhan, S., Mckinnon, R., Fortney, C., Divine, G., Janakiraman, N. Henry Ford Health System, Detroit, MI

Background: Stem cell dose for transplant is determined by CD34 although T cells are co-infused. A clear association of CD3 with clinical outcome is not established. The dose of CD3 is usually not taken into consideration except in T cell depleted transplantation. We did a retrospective analysis to study the effect of CD3cell infused on mortality, relapse, graft versus host disease (GVHD) and engraftment.

Methods: 161 patients with allogeneic stem cell transplantation, peripheral (PSCT) and marrow, were identified from the BMT Registry at Henry Ford Health System between 1999 and 2009. We classified disease risk into 2 categories; Low risk which includes acute leukemia and lymphoma in first complete remission or chronic myeloid leukemia in chronic phase. All others were considered as high risk disease. Engraftment is defined as absolute Neutrophil count (ANC) of 500/mm3and platelets as 20,000/mm3 per CIBMTR criteria. Acute GVHD was graded according to Glucksberg system.

Results: Among 161 patients, 137 patients (85%) had PSCT and 24 (15%) had marrow transplant. Mean age was 47.72 (19-71). Patients with high risk disease were 137 (85%), low risk disease were 24 (15%). 147 (91%) received myeloablative regimens while 14 (9%) received a non-myeloablative one. Source of transplant was related in 117 patients (73%), unrelated in 44 (27%). 120 patients (75%) had a good match. Mean dose of CD34 infused was 5.75×10^6/kg (1-22.3) while mean for CD3 infused was 1.23×10^8/kg (0-13.4). There was a statistically significant adverse correlation between CD3 infused and overall survival (p = 0.013). This was true even when adjusted for age, match status and disease risk (HR = 1.167,p = 0.010). We did not find association between CD3 infused and grade II-IV GVHD or relapse. There was very small negative correlation between CD3 infused and days to ANC 500 (r = -0.14, p = 0.089). After adjustment for the few outliers, the partial correlation was -0.15, p = 0.086. There was also a modest positive correlation with Platelet 20000, r = 0.36, p < 0.001. After adjustment, the correlation was 0.37, p < 0.001.

Conclusion: In this small group of 161 allo-stem cell transplant, we found that the dose of CD3 infused significantly affected the outcome by decreasing survival and modestly affecting days to engraftment. This supports the need to monitor CD3 and to be aware of it when deciding CD34 dose to be infused. Since this is a small group, further studies involving larger cohort of patients are needed.

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APHERESIS AND TRANSPLANT OF HEMATOPOIETIC PROGENITOR CELLS (HPC) FROM ALLOGENEIC DONORS ≥60 YEARS OF AGE

Janssen, W.E., Ayala, E., Field, T., Kharfan-Dabaja, M., Ochoa, L., Rahn, D., Hackett, M., Coyle, D., Anasetti, C., Fernandez, H.F. Moffitt Cancer Center, Tampa, FL

There has been reluctance to collect apheresis HPC allografts from donors of age 60 or greater. This is predicated on concern over relative frailty, poor venous access, reduced potential for HPC mobilization, and reduced potential for stable engraftment of HPC transplant. We have expanded our transplant eligibility into patients beyond the age of 60, with the concomitant acceptance of sibling donors of similar age. Herein we review 104 consecutive sibling donors, 20 of whom were of age ≥60 years at the time of collection. All donors were collected beginning on day 5 of 10mcg/Kg/day of G-CSF mobilization. Apheresis was performed using Caridian Spectra instruments, and the volume of blood processed was adjusted to target a CD34 dose of 5-10 million per Kg of recipient weight. We have compared these two groups of donors for total blood volumes (TBV) processed, CD34 cells recovered per Kg of recipient weight, and CD34 cells recovered per TBV apheresed, using Student's T-test. Comparison of rates of failure to recover 5 million CD34/Kg-recipient, requiring greater than one collection, requiring a catheter, and of having a grade 3 or 4 reaction to apheresis were performed using Fisher's exact test, and comparison of engraftment rates was performed using the log-rank statistic. Our findings are presented in the table. These results demonstrate that donors of age ≥60 years may be successfully collected by apheresis following G-CSF mobilization, and that the resultant grafts can be expected to produce successful transplants. There no greater rate of toxicity or need for catheter insertion associated with the collections in the older age group. There was, however, a clear trend to reduced mobilization of CD34+ cells, as reflected in an apparent need for more collections, and statistically fewer CD34+ cells per blood volume leukopheresed. In spite of this, sufficient cells to produce functional grafts were collected from all donors, although a limited number of donors in both age categories failed to collect a full 5e + 6 CD34/Kg. We conclude that in the context of an aging demographic, allograft donors of age ≥60 may be successfully employed for HPC collection. Further, we propose that the application of plerixafor in ≥60 year old donors should be investigated in the context of a growing need to collect allografts from donors in this age group.

	Age < 60 (n = 86)	Age > 60 (n = 20)	p
Blood volumes (Mean ± Std)	5.0 ± 3.3	6.1 ± 3.1	0.17
CD34/RecipKg E6 (Mean ± Std)	8.3 ± 3.1	5.8 ± 1.7	0.001
CD34/Blood vol E7. (Mean ± Std)	18.7 ± 11.8	11.0 ± 7.6	0.006
< 5E6 CD34/Kg Collected (n)	6	3	0.25
> 1 collection (n)	15	7	0.087
Catheter required (n)	25	6	0.59
Grade 3+ pheresis complications	2	3	0.047
ANC500 Median days (Min-Max)	16 (10-28)	16 (13-75)	0.14
Plt20 K Median days (Min-Max)	16 (8-77)	16 (13-89)	0.30